REMARKS

Claims 80 and 81 have been amended. Claims 1-26, 33, 35-53, 56, 60-79 and 82 are canceled. Applicant reserves the right to pursue these claims in this and in other applications.

Claims 27-32, 34, 54-56, 57-59 and 80-82 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Deihl (WO 94/13280) in view of Fassberg et al (EP 0656206) and further in view of Kanios et al (U.S. Patent No. 5,719,197) or alternatively in view of the Physicians' Desk Reference, 1995 (PDR).

Independent claims 80 and 81 recite methods of administering an effective amount of a pharmacologically active compound to a mammal comprising spraying the oral mucosa of the mammal with a propellant free buccal spray composition containing a pharmacologically active compound dissolved in a pharmacologically acceptable solvent. According to independent claims 80 and 81, the active compound comprises a benzodiazepine, a clozapine, phenytoin or a pharmaceutically acceptable salt thereof. Independent claim 80 further recites "wherein a therapeutically effective amount of the active compound is absorbed through the oral mucosa of the mammal to the mammal's systemic circulatory system," and "wherein a therapeutic effect of the active compound administered by the act of spraying is achieved with a first amount of the active compound, the first amount being less than a second amount of the active compound necessary to achieve the therapeutic effect when passed through a gastrointestinal tract of the mammal." Independent claim 81 further recites "wherein a therapeutically effective amount of the active compound is absorbed through the oral mucosa of the mammal to the mammal's systemic circulatory system," and "wherein a period of time for onset of a therapeutic effect of an amount of the active compound administered by the act of spraying is less than a period of time for onset of the therapeutic effect for the amount of the active compound when passed through a gastrointestinal tract of the mammal."

The Office Action asserts that Deihl provides "general teachings of formulations for buccal mucosal administration" (Office Action at 4). The Office Action acknowledges, as it must, that Deihl fails to disclose any of the active compounds recited by any of the claims, and also fails

to disclose the use of the presently claimed solvents or amounts, including polyethylene glycol or non-polar solvents. Moreover, Deihl fails to achieve "absorption" of a "therapeutically effective amount" of any active, and does not teach any methods "wherein a therapeutic effect of the active compound administered by the act of spraying is achieved with a first amount of the active compound, the first amount being less than a second amount of the active compound necessary to achieve the therapeutic effect when passed through a gastrointestinal tract of the mammal;" or "wherein a period of time for onset of a therapeutic effect of an amount of the active compound administered by the act of spraying is less than a period of time for onset of the therapeutic effect for the amount of the active compound when passed through a gastrointestinal tract of the mammal," as recited by the present claims.

Based on the alleged "general teaching" of Deihl, the Office Action asserts that it would have been obvious to "have looked in the art for other specific solvents suitable for spray formulations of liquid carriers, as taught by Fassberg et al., with reasonable expectations of successfully preparing suitable formulations for various therapies." (Office Action at 4-5). The Office Action also asserts that "it is obvious to one of ordinary skill in the art to have substituted any suitable active agent for the analgesics of Deihl's buccal spray formulations as...taught by Kanios et al or Physicians' Desk Reference." (Office Action at 4-5, emphasis added).

Thus, the Office Action is premised on the PTO's reading of Deihl as a "general teaching" from which one may allegedly extrapolate to multiple other solvents and amounts, and to other pharmaceutically active agents, and do so with a reasonable expectation of success. Remarkably, this reasoning is based in part on Fassberg et al., which is not directed to propellant-free sprays as claimed, and on Kanios or the PDR, which are not directed to buccal sprays at all. Aside from the shortcomings of these secondary references, Deihl itself is far from a "general teaching" of buccal spray formulations from which one of ordinary skill at the time of the present invention would have expected much of anything at all, much less that one of ordinary skill would have been motivated in any way to modify Deihl with any reasonable expectation of successfully achieving the presently claimed methods.

More specifically, at the time of the present invention, Deihl would not have been considered a credible teaching and, for the reasons discussed below, would not have been relied upon in any capacity by those skilled in the art at the time that the present invention was made. Deihl purports to teach a sprayable analgesic composition where an analgesic is capable of being absorbed into the bloodstream through the buccal mucosa. Deihl's composition includes ibuprofen or acetaminophen and aqueous ethanol. Deihl states that for treatment of a head ache, a patient sprays four measured sprays into the mouth. Each spray is 50 microliters and contains 1 milligram of acetaminophen or ibuprofen. This treatment is repeated once after five minutes. That is, Deihl teaches a total dose of 4-8 milligrams of acetaminophen or ibuprofen. Deihl at 5.

Even assuming 100 percent bioavailability, however, those of ordinary skill in the art would readily appreciate that Diehl's 4-8 milligram dose of acetaminophen or ibuprofen is not even remotely therapeutically effective. According to GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 10th ed., the oral dosage for acetaminophen is 320 to 1000 milligrams for adults and 40 to 480 milligrams for children with about 88% bioavailability. For ibuprofen the oral dosage for adults is 400 milligrams for mild pain to as much as 3200 milligrams for arthritis, with about 80% bioavailability. Thus, even assuming 100% bioavailability, a patient receiving Deihl's formulation would receive only 4-8 milligrams of active agent, a tiny fraction of what is required for any therapeutic effect. Accordingly, Deihl can not teach a method by which a therapeutic effect is achieved at all, much less one that is achieved with a smaller dose than that needed when the active compound passes through the gastrointestinal tract. A patient would need to administer a completely unworkable number of spray activations of Deihl's formulation to realize any potential therapeutic effect, but by that point the volume and fluid sprayed would be so great as to result in swallowing and thus avoid mucosal absorption. Therefore, one of ordinary skill in the art would have readily appreciated that Deihl's spray composition and method is unworkable and ineffective.

One of ordinary skill in the art would also have appreciated that Deihl's ineffective spray teachings were quite consistent with the state of the art at the time the present invention was made. Those skilled in the art generally perceived buccal administration as an ineffective and unworkable

delivery method. For example, REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY, 19th ed. (1995) at 710, states that "when only small amounts of drugs are required to gain access to the blood, the buccal route may be satisfactory, providing the physicochemical prerequisites for absorption by this route are present in the drug and dosage form. Only a few drugs may be given successfully by this route." (Emphasis added). Further, nothing in the prior art or cited references teaches or suggests a method of buccal administration providing faster onset of the therapeutic effect or the ability to achieve a therapeutic effect with a smaller dose than that provided when an active compound passes through the gastrointestinal tract, for example, when an active compound is administered by oral tablet.

This well accepted view of buccal administration was based in part on the belief that the relatively rapid clearing of the mouth by swallowing limited the buccal absorption phase to between about 5-10 minutes. Therefore, it was understood that the amount of drug delivered would be very small causing the blood plasma levels of dugs administered buccally to rise slowly. Thus, buccal administration was generally disfavored and thought to be an ineffective and unworkable delivery method. Consequently, the disclosure of Deihl itself, as well as the general understanding in the art, were completely inconsistent with the Office Action's assertions that Deihl provides a general teaching from which one of ordinary skill would have been motivated to extrapolate to diverse pharmaceutical actives and solvents, much less to do so with any expectation of success in administering a pharmaceutically effective amount of such actives via oral absorption of a buccal spray.

Furthermore, even if Diehl could be properly combined with the secondary references, the combination still would not provide all elements of the claims as amended, since Diehl (the only oral spray cited) does not itself disclose or achieve absorption of any therapeutically effective amount, much less achieve the other requirements and characteristics of the claimed methods.

In addition, Fassberg et al. relates to an inhalation aerosol, which is a propellant-containing spray or powder formulation for oral and/or nasal administration. Fassberg et al. does not disclose or suggest any propellant-free method for the delivery of an active agent by spraying

the buccal mucosa of a mammal. Fassberg et al. clearly does not teach or suggest buccal administration of any actives.

According to the PTO, it would have been obvious to modify Diehl with the solvents disclosed by Fassberg et al. (Office Action at 4-5.) To the contrary, one of ordinary skill would not have used the Fassberg et al. solvents to modify the formulations of Diehl, because Fassberg et al. explains that the solvents used in its inhalation formulations are only present to facilitate the propellant. Diehl has no propellant and the present claims exclude propellants. Accordingly, one of ordinary skill in the art would not have been motivated to modify Diehl with the teachings of Fassberg et al., for this additional reason.

One of ordinary skill in the art also could not have been motivated to modify Diehl, which provided for no therapeutic effect, with the actives of Kanios et al. or the PDR, with any expectations of success in achieving the methods recited by the presently pending claims. Kanios et al. refers to an intermediate composition that is made into a "finished dosage form" by applying a flexible backing which further defines the size and shape of the finished dosage form, which is, among other things, occlusive to water permeation in vivo. Kanios et al. is entirely unrelated to a buccal spray method for transmucosal administration. The PDR simply lists various active compounds and, like Kanios et al., is entirely unrelated to a buccal spray method for transmucosal administration.

Consequently, none of the prior art of record alone or in any combination teaches all elements of the present Applicants' independent claims. In particular, none of the art alone or in combination teaches transmucosal absorption of a therapeutically effective amount of any active compounds, much less those claimed here, by spraying the oral mucosa or a method of buccal administration providing faster onset of the therapeutic effect or the ability to achieve a therapeutic effect with a smaller dose than that provided when the active compound passes through the gastrointestinal tract. Moreover, the state of the art, including Remington: *The Science and Practice of Pharmacology*, teaches away from the Applicants' invention as presently claimed. Remington demonstrates that "only a few drugs may be given successfully by [the buccal spray] rate" and

Deihl's method was apparently unsuccessful. Furthermore, in addition to the general but significant bias in the art (at the time of the invention) against buccal spray administration, Applicants have discovered surprisingly beneficial results from their use of a buccal spray which further supports the non-obviousness of the claimed invention. See, e.g., specification at paragraph [0003] and [0025]. For at least these reasons, Applicants respectfully request that this § 103 rejection be withdrawn.

Claims 27-32, 34, 54-56, 57-59 and 80-82 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Fu (WO9303751) in view of the Physician's Drug Reference (PDR). This rejection is respectfully traversed.

The Office Action also improperly uses Fu as a "general teaching" from which one of ordinary skill could have allegedly extrapolated to any other pharmaceutical active, and have done so with at least a reasonable expectation of success, based on "the general teachings of formulations for buccal mucosal administration of Fu " (Office action at 6). The Office Action is mistaken, as Fu is anything but a general teaching that would have motivated one of ordinary skill to look to the PDR with any expectation of success and the general state of the art at the time of the present invention was to the contrary.

As discussed above, those skilled in the art perceived buccal administration as an ineffective and unworkable delivery method. See, REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY, 19th ed. (1995) at 710. Fu refers to compositions for the sublingual delivery of specific polypeptides that are normally degraded upon oral administration. Fu is specifically directed to the administration of these polypeptides because they cannot be orally ingested. These polypeptides are very limited in scope. Fu only present examples of formulations containing leuprolide acetate and deslorelin acetate, which is closely related to leuprolide acetate. At most, Fu establishes that buccal administration can be used for specific polypeptides and only when a permeation enhancer is employed. See e.g., Fu at 10-12 (showing low bioavailability for exemplary formulations, less than 25% bioavailability for all but one formulation). This underscores the general state of the art regarding the problem with buccal sprays as described by Remington.

The examples provided by Fu are limited to two closely related polypeptides that can not be administered by oral ingestion. The presently claimed actives are capable of being administered through the G.I. tract and the amended claim language expressly addresses this capability. Thus, Fu would not have been viewed as a "general teaching" for successful buccal spray administration of the currently recited pharmaceutical actives. Therefore, one of ordinary skill in the art would not have been motivated to modify Fu with the pharmaceutical actives of the PDR, or expect that such a combination would have been viable for administering a pharmacologically effective amount of the claimed actives, nor of achieving the claimed characteristics wherein "a therapeutic effect of the active compound administered by the act of spraying is achieved with a first amount of the active compound, the first amount being less than a second amount of the active compound necessary to achieve the therapeutic effect when passed through a gastrointestinal tract of the mammal" or "wherein a period of time for onset of a therapeutic effect of an amount of the active compound administered by the act of spraying is less than a period of time for onset of the therapeutic effect for the amount of the active compound when passed through a gastrointestinal tract of the mammal."

None of the prior art of record alone or in any combination teaches all elements of the present Applicants' independent claims. In particular, none of the art teaches transmucosal absorption of an effective amount of the claimed actives by spraying the oral mucosa, as required by all of the pending claims. And none teaches that "a therapeutic effect of the active compound administered by the act of spraying is achieved with a first amount of the active compound, the first amount being less than a second amount of the active compound necessary to achieve the therapeutic effect when passed through a gastrointestinal tract of the mammal" or that "a period of time for onset of a therapeutic effect of an amount of the active compound administered by the act of spraying is less than a period of time for onset of the therapeutic effect for the amount of the active compound when passed through a gastrointestinal tract of the mammal." Furthermore, in addition to the general but significant bias in the art (at the time of the invention) against buccal spray administration, that the Applicants have discovered surprisingly beneficial results from their use of a buccal spray further supports the non-obviousness of the claimed invention. See, e.g.,

specification at paragraph [0003] and [0025]. For at least these reasons, Applicants respectfully request that this rejection be withdrawn.

Double Patenting

Claims 27-32, 34, 54-56, 57-59 and 80-82 are rejected on the grounds of non-statutory obviousness-type double patenting as being unpatentable over claims of various commonly owned U.S. patents, and are also provisionally rejected over claims of several co-pending applications. As the claims of the present application, as well as those of the co-pending applications are subject to change, Applicants respectfully request that these rejections be held in abeyance until such time as this application is otherwise in a condition for allowance.

Except for the double patenting issues, each of the presently pending claims in this application is believed to be in a condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims. Should the Examiner believe that anything further may be requested to place this application in even better form for allowance, the Examiner is cordially invited to telephone the undersigned attorneys for Applicants.

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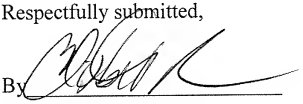
Respectfully submitted,

By 

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